



Phenotypic error threshold: additivity and epistasis in RNA evolution

Nobuto Takeuchi*

Pieter Poorthuis

Paulien Hogeweg

*takeuchi_nobuto@yahoo.co.jp

Theoretical Biology/Bioinformatics

Utrecht University



Evolutionary dynamics in view of



- Mutation-selection on the same level

For example:

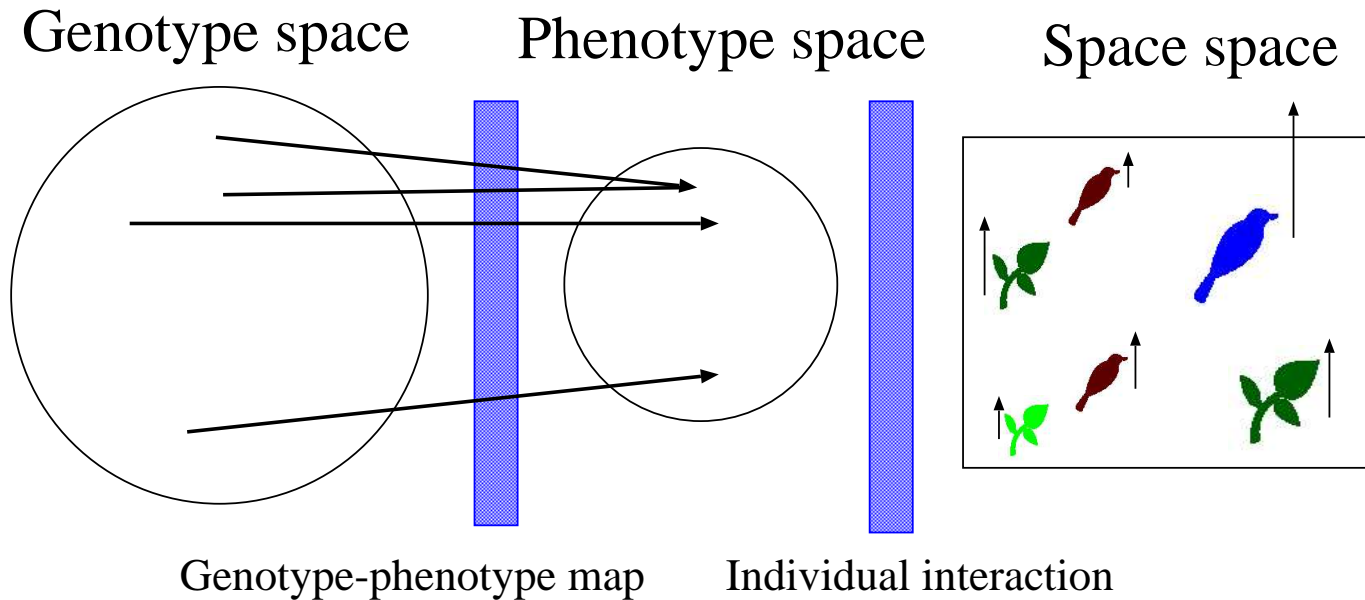
- Phenotype level
 - Game theory
 - Adaptive dynamics
- Genotype level
 - Population genetics
 - Quantitative population genetics
- Mutation & selection are in the separated time scales



Evolutionary dynamics in view of



- Genotype-phenotype-individual_interaction



- Time scales of mutation and selection are not separated.



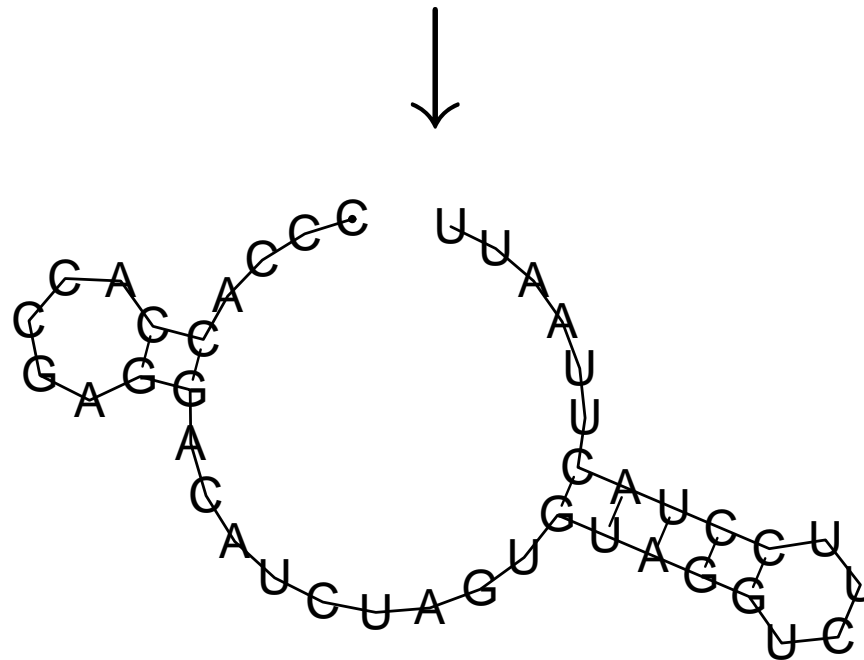
RNA folding

as a genotype-phenotype map

RNA sequence → Secondary structure

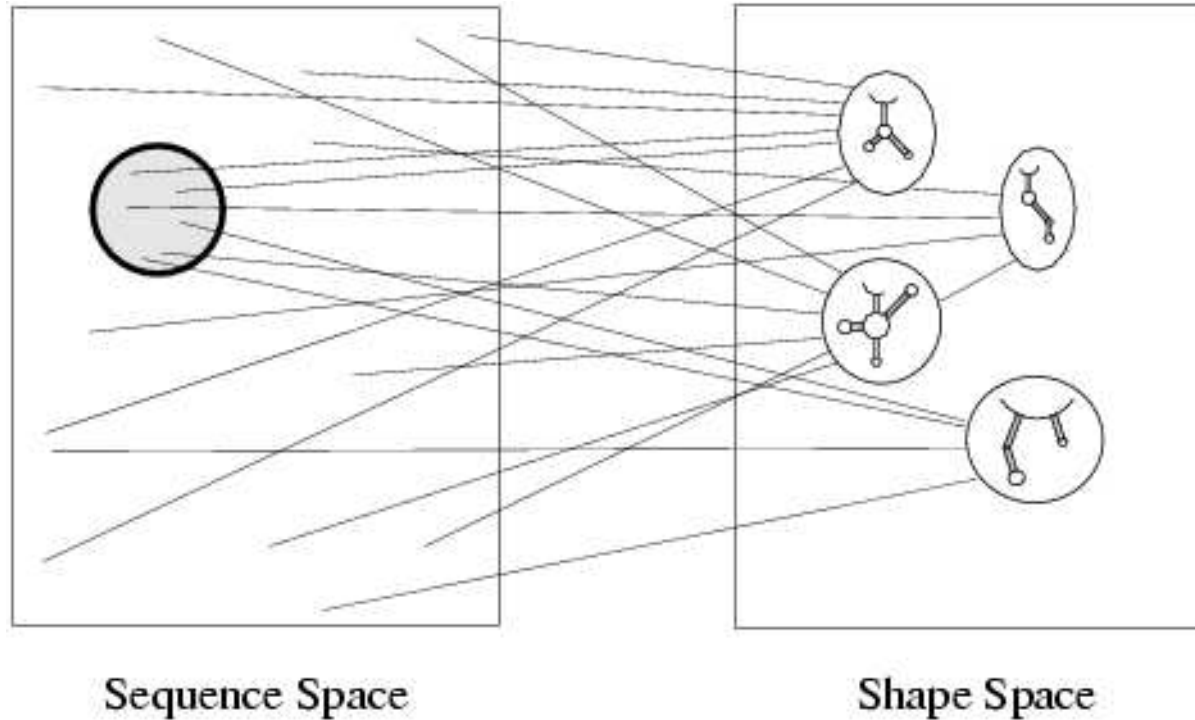
(*e.g.*)

CCCACCACCGAGGACAUCUAGUGUAGGUCUUCCUACUUAUUU



RNA folding

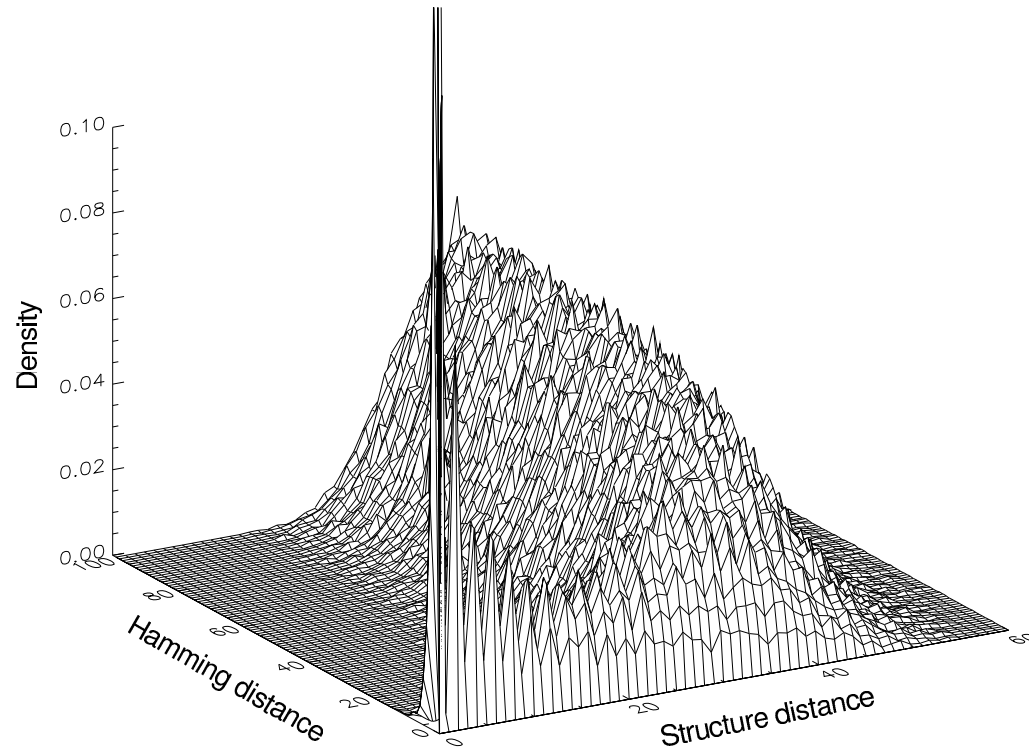
as a genotype-phenotype map



[Schuster P *et al.* (1994) Proc R Soc Lond B]

Features of RNA folding G-P map

- Non-linearity

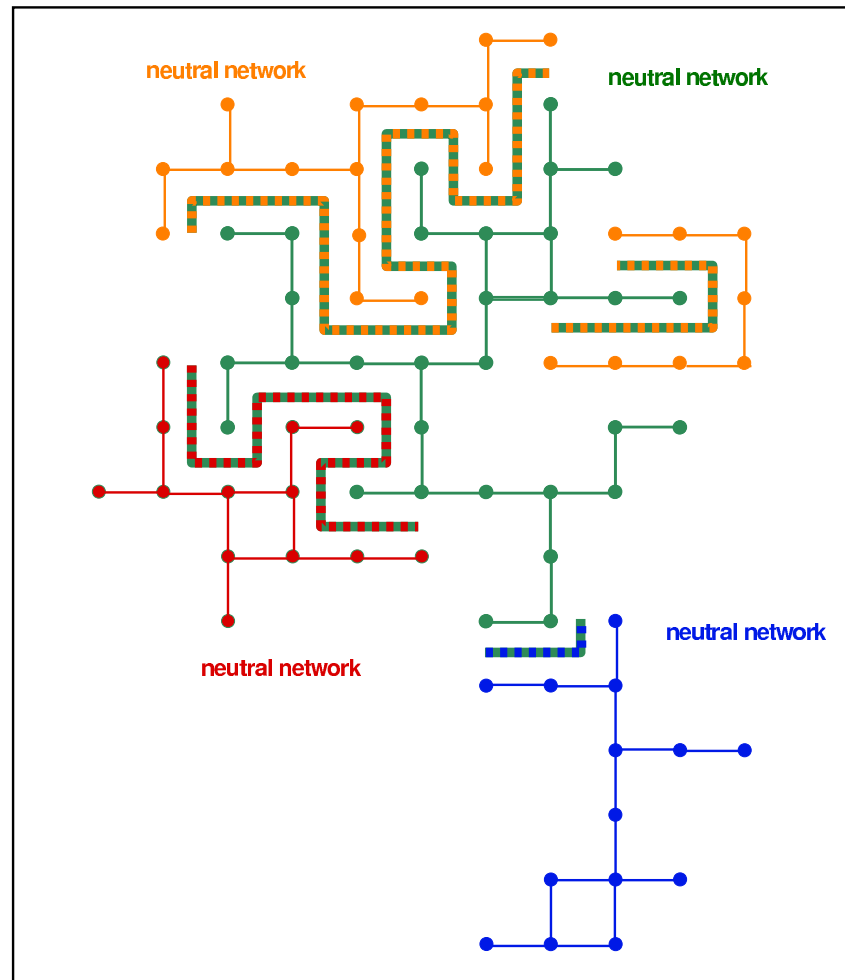


[Huynen MA *et al.* (1993) JTB]

[Schuster P *et al.* (1994) Proc R Soc Lond B]

Features of RNA folding G-P map

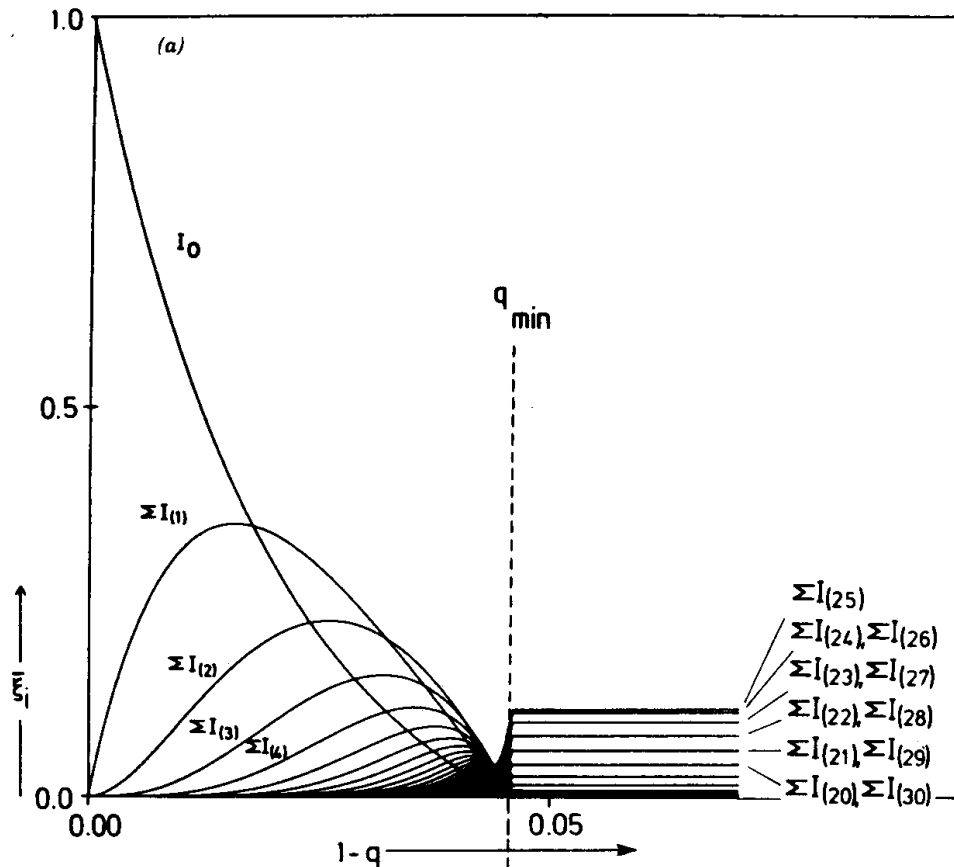
● Neutral network



[Fontana W. (2002) BioEssays]

Selection-mutation in the same time scale

Quasi-species & error threshold



[Eigen M *et al.* (1989) Adv Chem Phys]

$$q > (1/\sigma)^{1/N}$$
$$N < \frac{\ln(\sigma)}{1-q}$$

N : sequence length

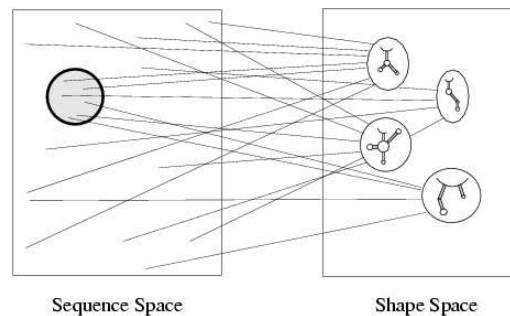
q : replication accuracy/base

σ : superiority of the fittest

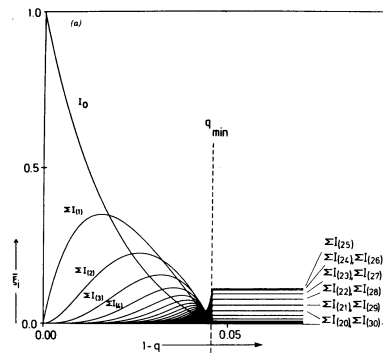
Combining two



- RNA folding genotype-phenotype map
Neutral networks.



- Mutation/selection dynamics; quasi-species theory
Error threshold

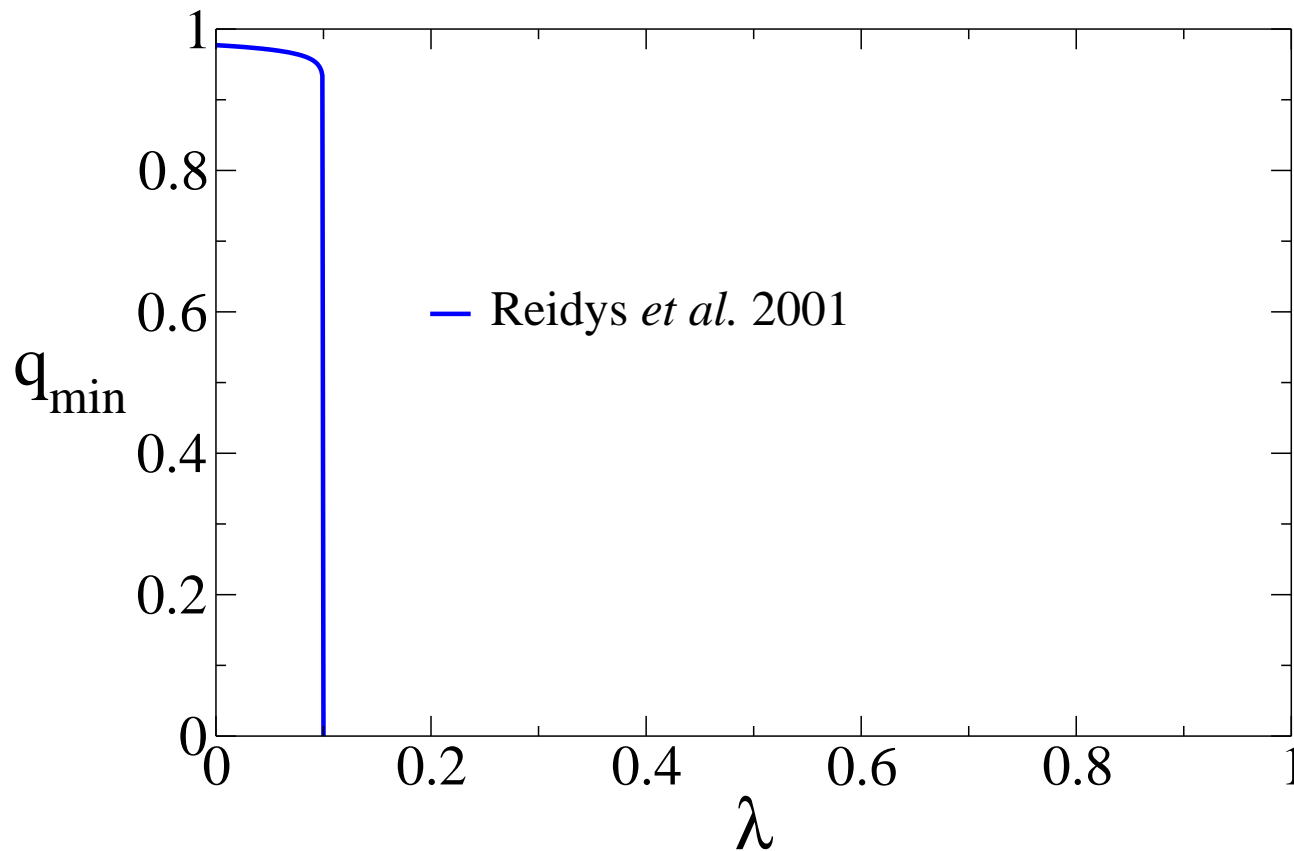


Mutation-selection dynamics in neutral networks



- Error-threshold disappears by mutational neutrality

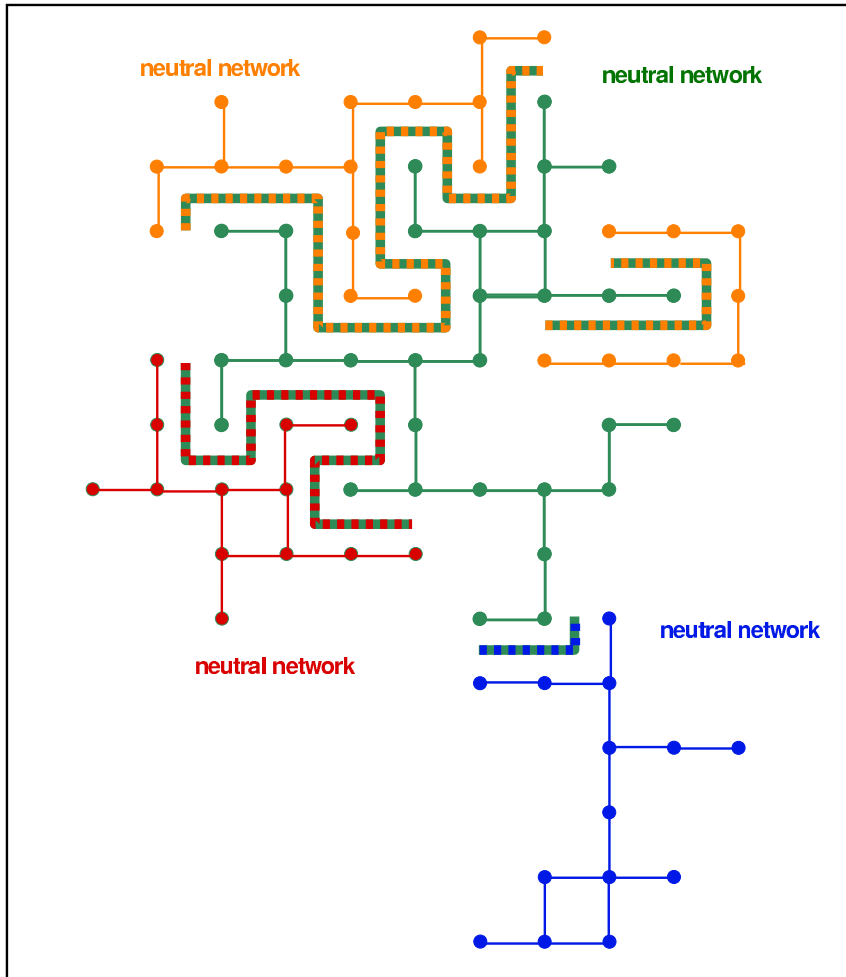
$$N=100, \sigma=10$$



[Reidys C *et al.* (2001) Bull Math Biol]



No unique fittest genotype



$$q > (1/\sigma)^{1/N}$$

$$N < \frac{\ln(\sigma)}{1-q}$$

N : sequence length

q : replication accuracy/base

σ : superiority of the fittest

[Fontana W. (2002) BioEssays]

Phenotypic error-threshold



- Error-threshold should be defined in terms of phenotype
 - if a genotype-phenotype map involves mutational neutrality.

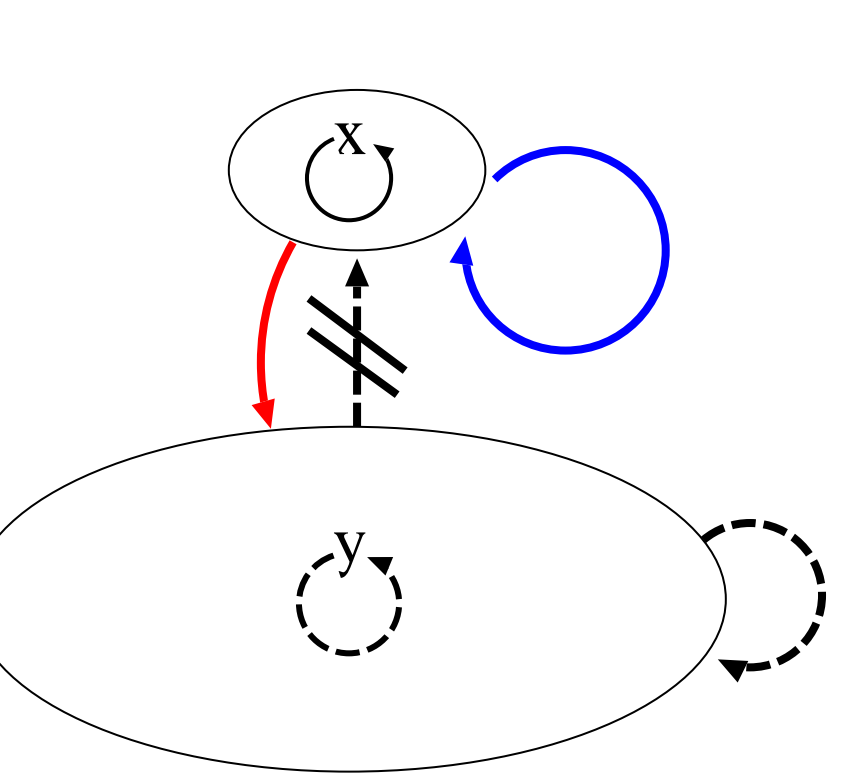
[Huynen MA *et al.* (1996) PNAS]



Analytical formulation of phenotypic error-threshold



- Simplification of quasi-species equation



x is master:

$$\begin{cases} \dot{x}_1 = \sum_{i \in N} Q_{1i} A_i x_i - D_1 x_1 - \Phi x_1 \\ \vdots \end{cases}$$

y is mutant:

$$\begin{cases} \dot{y}_n = \sum_{i \notin N} Q_{ni} A_i y_i \\ \quad + \sum_{i \in N} Q_{ni} A_i x_i - D_n y_n - \Phi y_n \\ \vdots \end{cases}$$



Analytical formulation of phenotypic error-threshold



- Our equations are

$$\text{master: } \dot{x} = \sigma Qx + \sigma(1 - Q)\Lambda x - Dx - \Phi x,$$

$$\text{mutant: } \dot{y} = y + \sigma(1 - Q)(1 - \Lambda)x - Dy - \Phi y$$

| | |
|-----------|---|
| Q | <i>Replication accuracy</i> |
| σ | <i>Growth rate of x (speed of replication)</i> |
| D | <i>Death rate</i> |
| Φ | <i>Dilution (the average fitness)</i> |
| Λ | <i>Fraction of neutral mutants</i> |



Analytical formulation of phenotypic error-threshold



- Our equations are

master: $\dot{x} = \sigma Qx + \sigma(1 - Q)\Lambda x - Dx - \Phi x,$

mutant: $\dot{y} = y + \sigma(1 - Q)(1 - \Lambda)x - Dy - \Phi y$

- Survival condition of x is

$$\sigma Q + \sigma(1 - Q)\Lambda > 1$$



Analytical formulation of phenotypic error-threshold



- Our equations are

$$\text{master: } \dot{x} = \sigma Qx + \sigma(1 - Q)\Lambda x - Dx - \Phi x,$$

$$\text{mutant: } \dot{y} = y + \sigma(1 - Q)(1 - \Lambda)x - Dy - \Phi y$$

- Survival condition of x is

$$Q_e \equiv Q + (1 - Q)\Lambda > \frac{1}{\sigma}$$





Additive assumption

- **Base substitutions act independently**
(& binomial assump.)

| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | ... | |
|--------------------------|---|--------|--------|-------------|-------------|--------|--------|-------------|-----|---------------|
| neutral substitution | C | A C | C | | | G | A | G U A | ... | λ |
| correct | A | U | G | C | A | U | G | C | ... | |
| deleterious substitution | G | G | A U | A U G | G C U | A C | C U | | ... | $1 - \lambda$ |



Additive assumption

- **Base substitutions act independently**
(& binomial assump.)

$$\begin{aligned} Q_e &= q^N + \sum_{d=1}^N \binom{N}{d} q^{N-d} (1-q)^d \lambda^d \\ &= \{q + \lambda(1-q)\}^N \end{aligned}$$

Additive assumption

- **Base substitutions act independently**
(& binomial assump.)

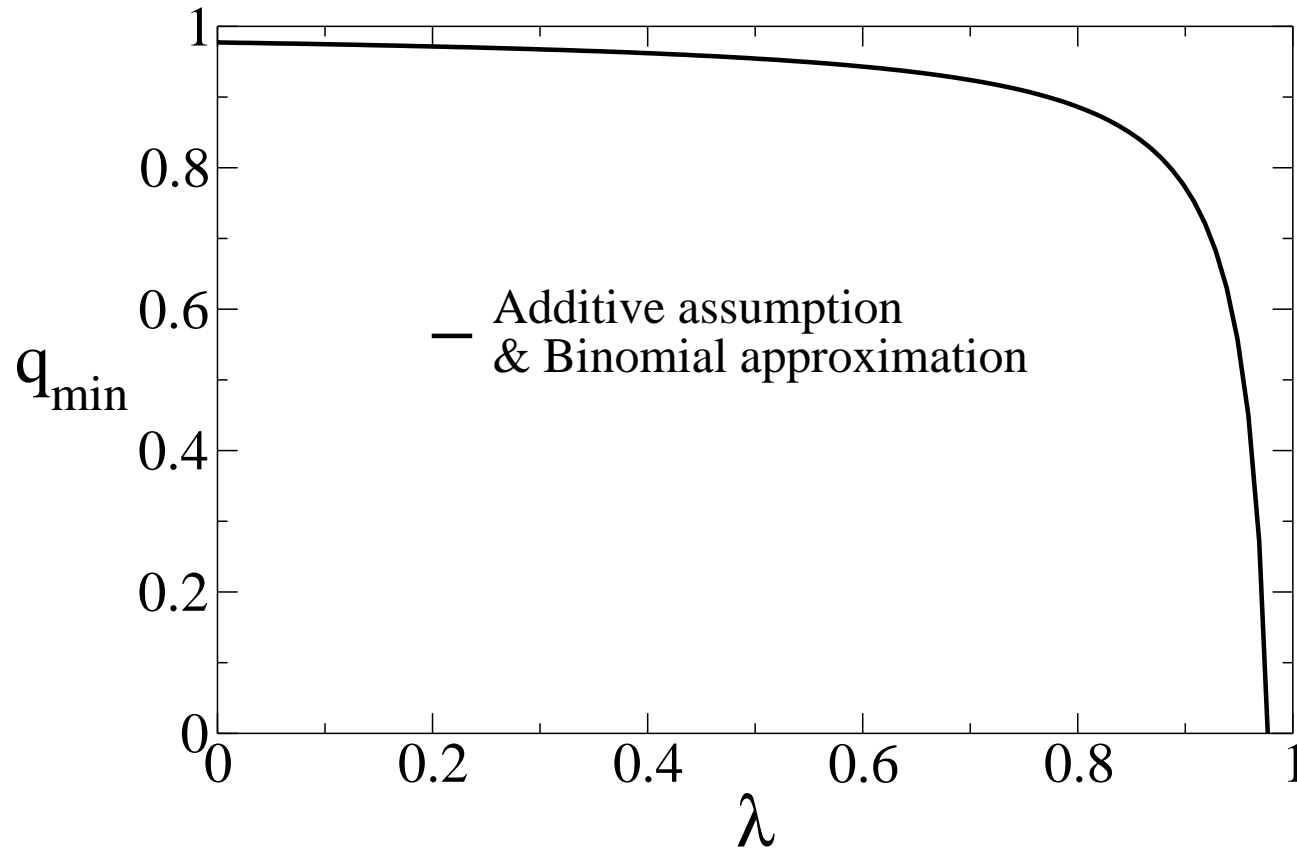
$$\begin{aligned} Q_e &= q^N + \sum_{d=1}^N \binom{N}{d} q^{N-d} (1-q)^d \lambda^d \\ &= \{q + \lambda(1-q)\}^N \end{aligned}$$

- **Phenotypic error threshold**

$$q > \frac{\sigma^{-1/N} - \lambda}{1 - \lambda}$$

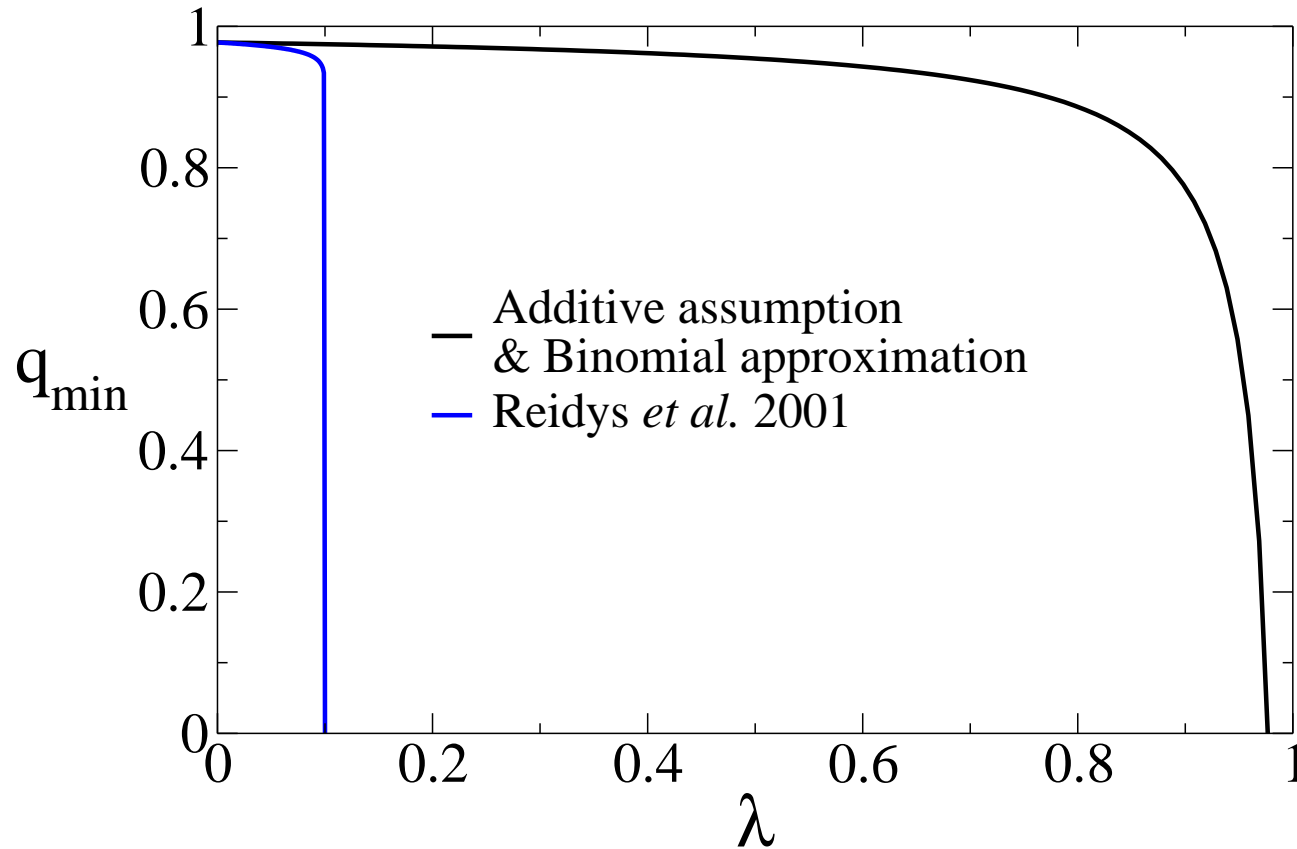
Phenotypic Error-threshold

$N=100, \sigma=10$



Phenotypic Error-threshold

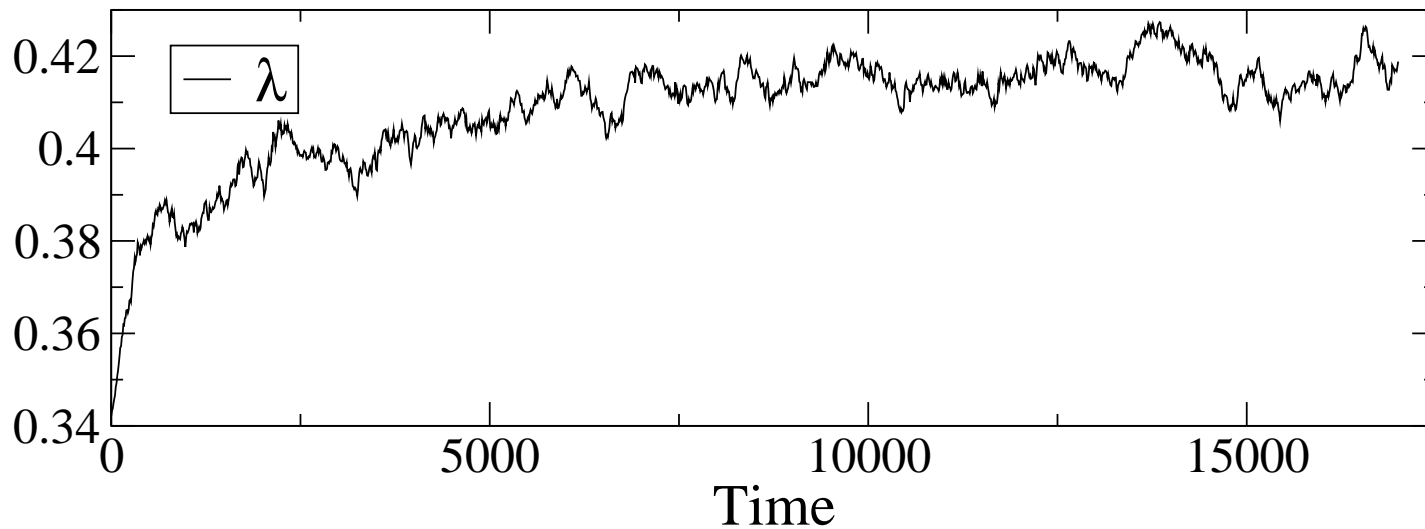
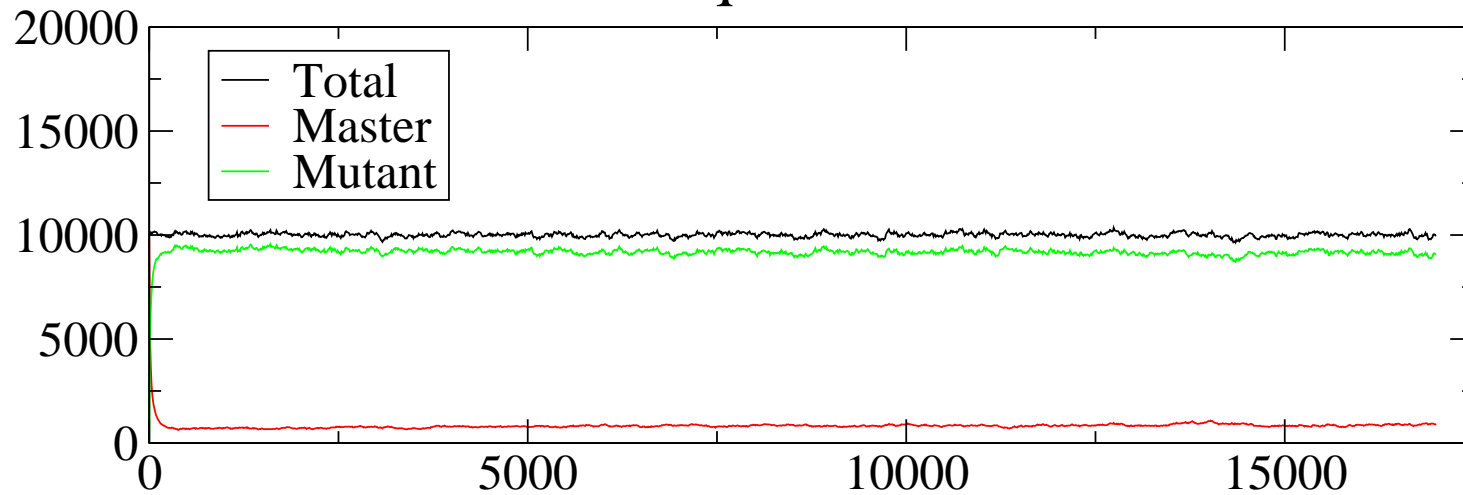
$N=100, \sigma=10$



Computer simulations of RNA evolution:

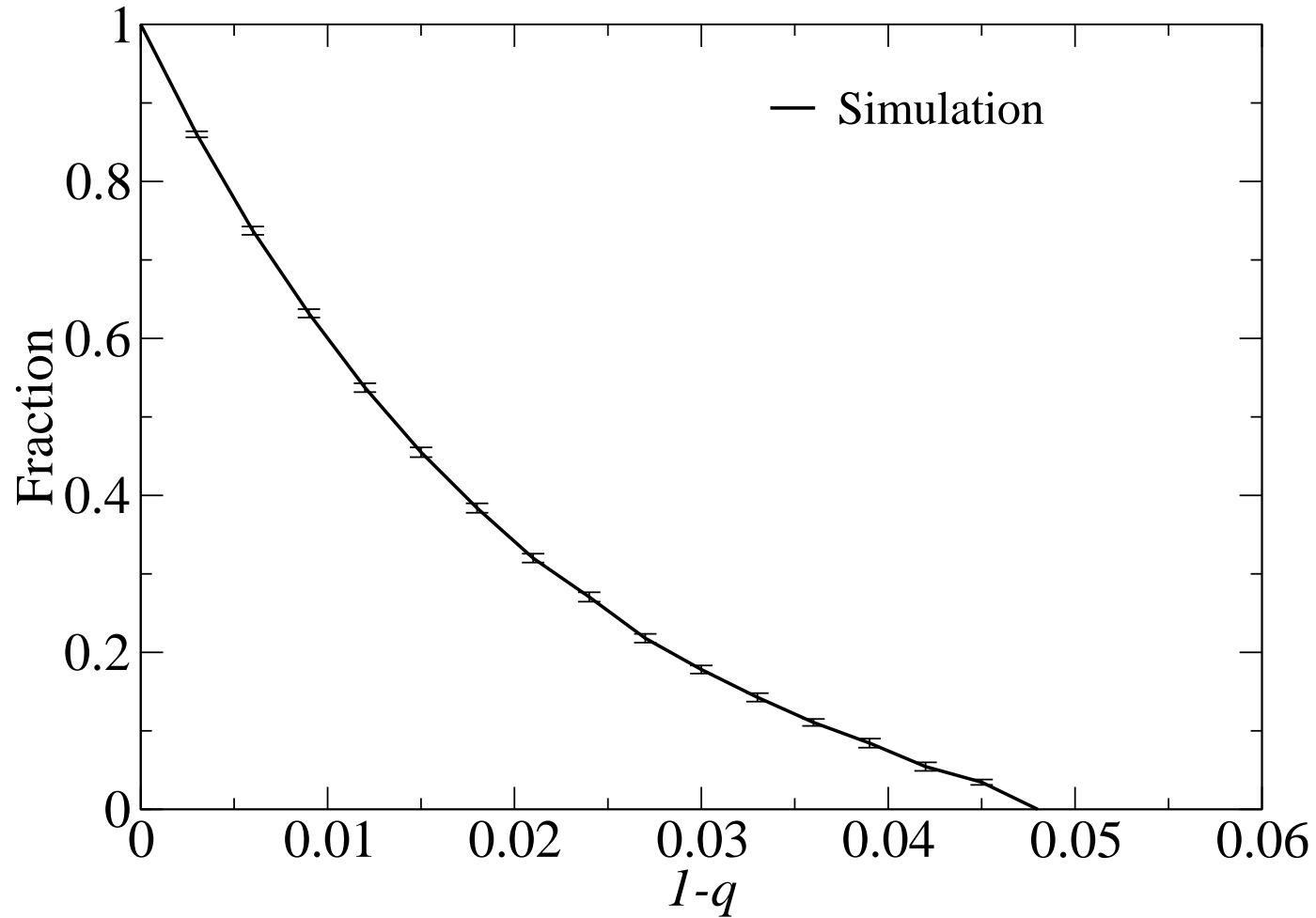
— An example run —

$1-q=0.039$



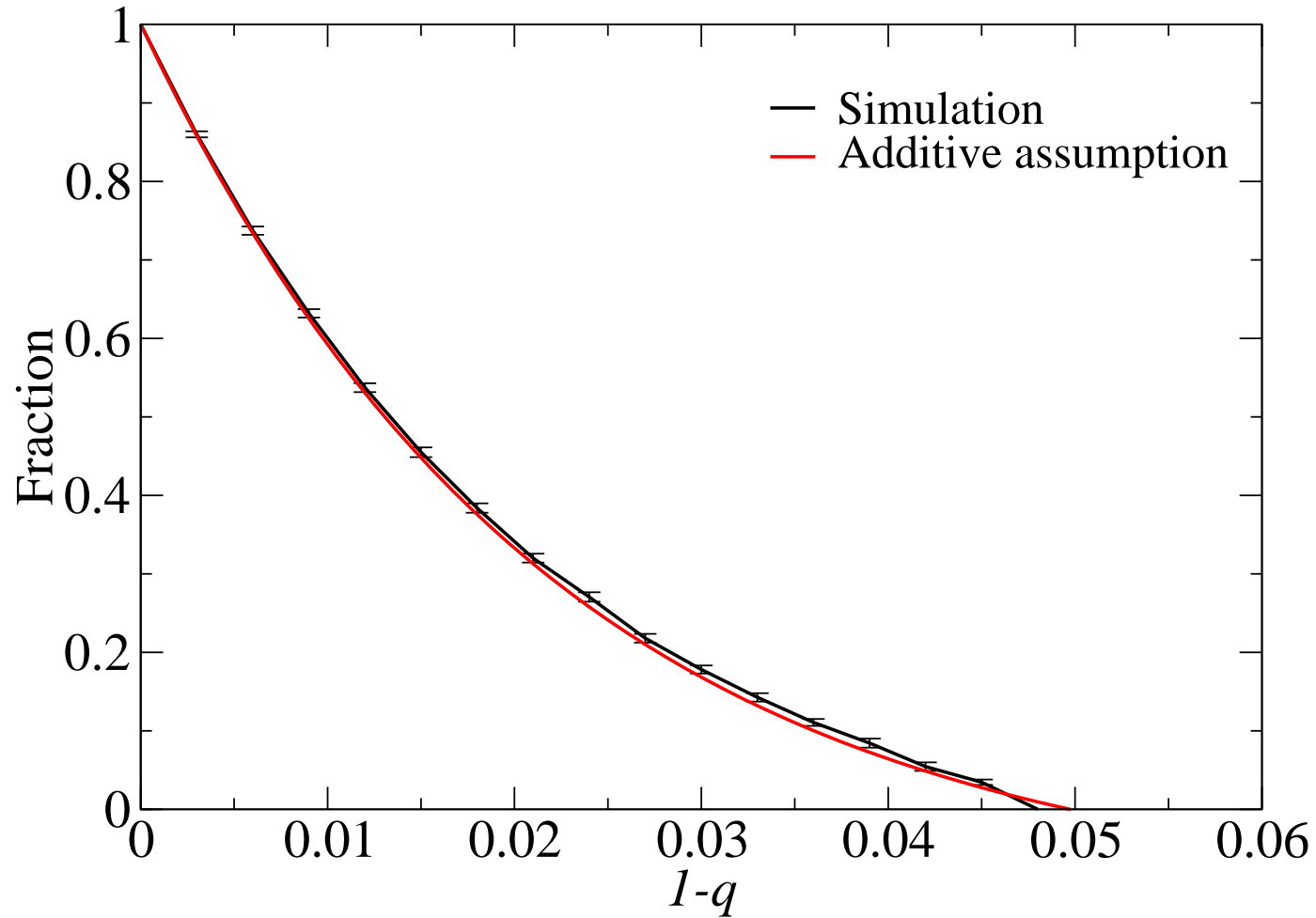
Computer simulations of RNA evolution:

—Simulation VS prediction—



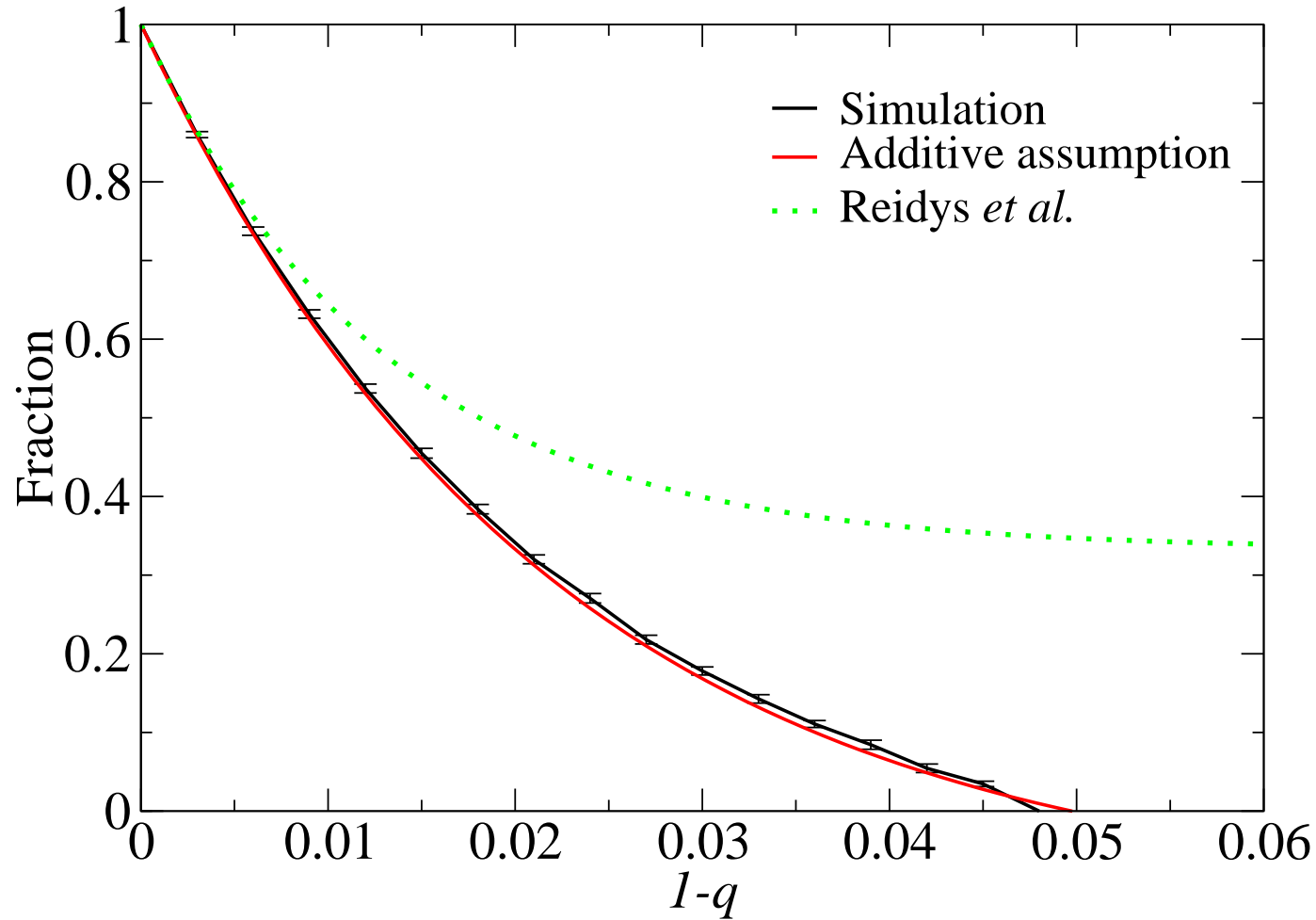
Computer simulations of RNA evolution:

—Simulation VS prediction—

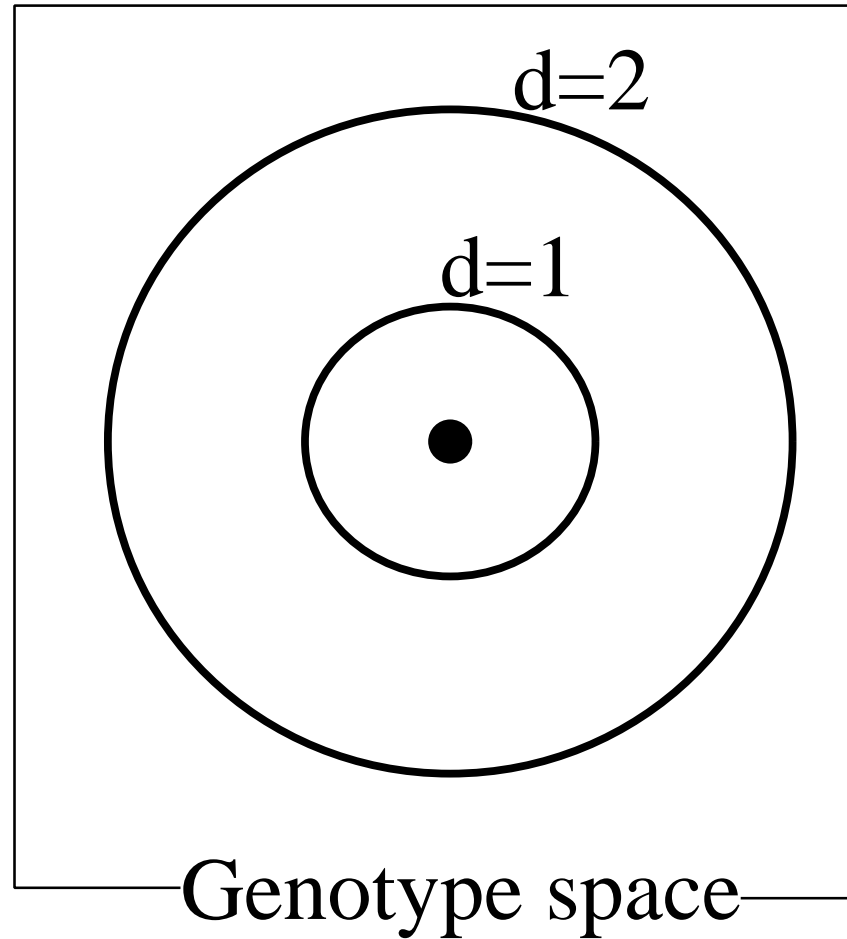


Computer simulations of RNA evolution:

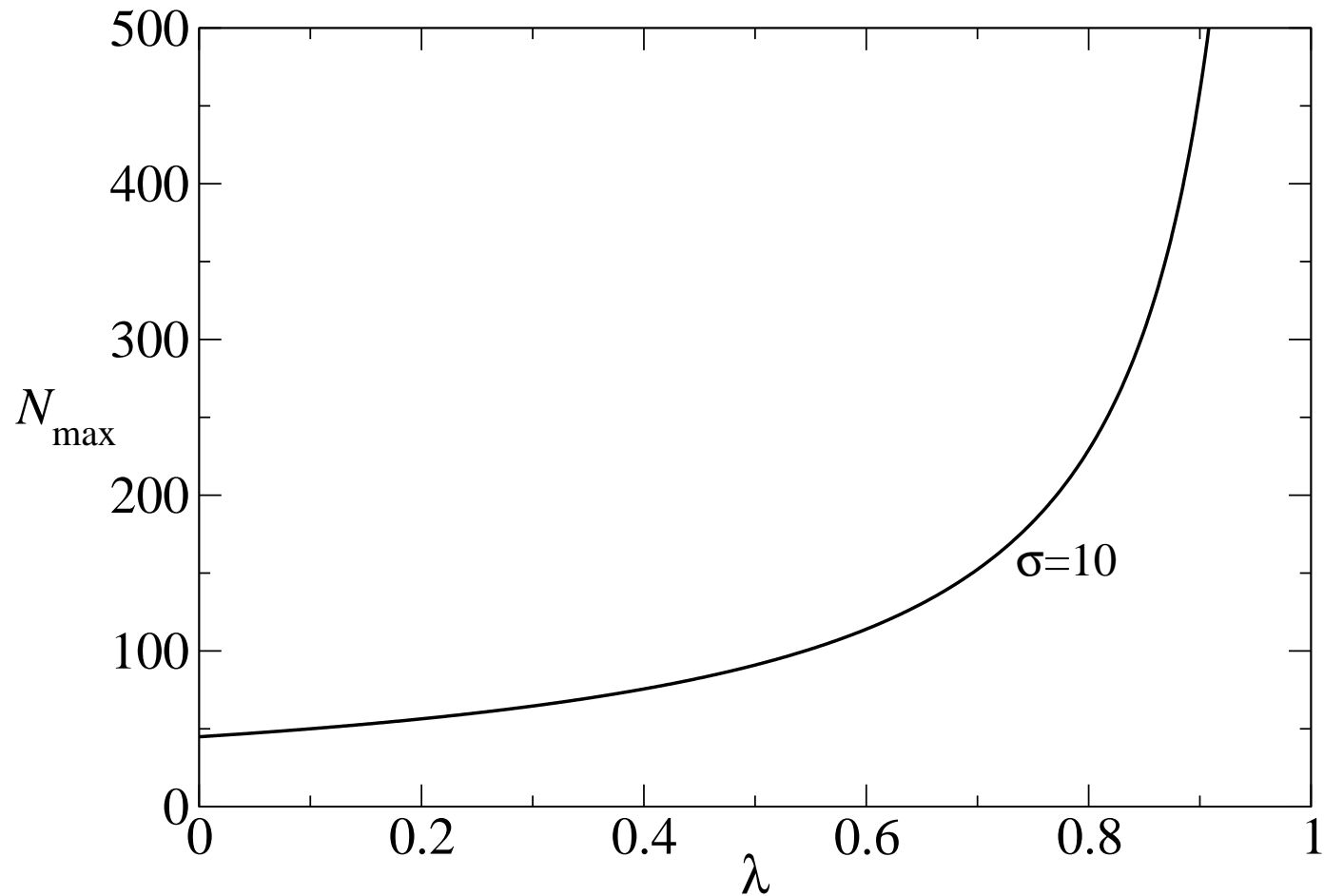
—Simulation VS prediction—



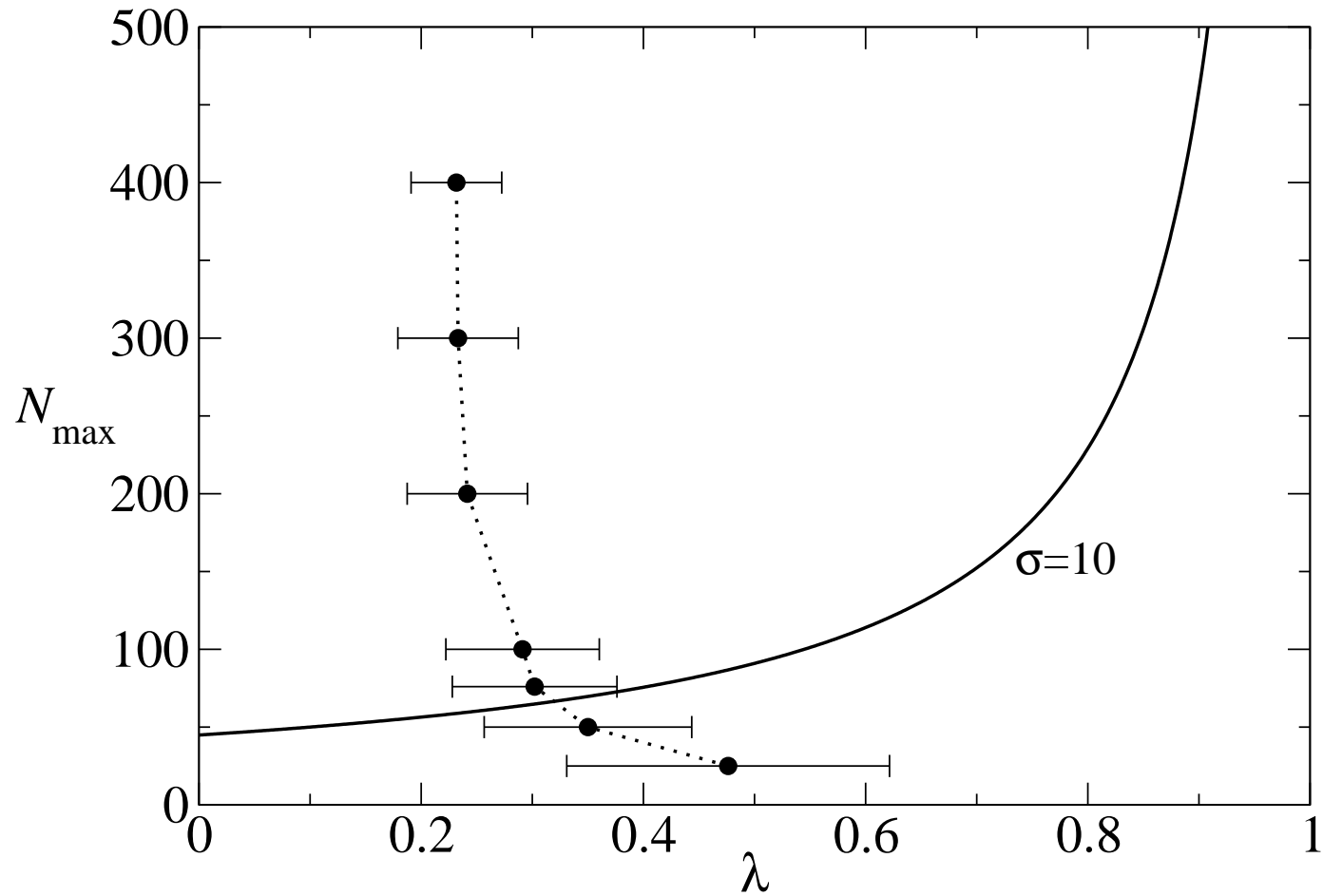
Comparison with other formalism



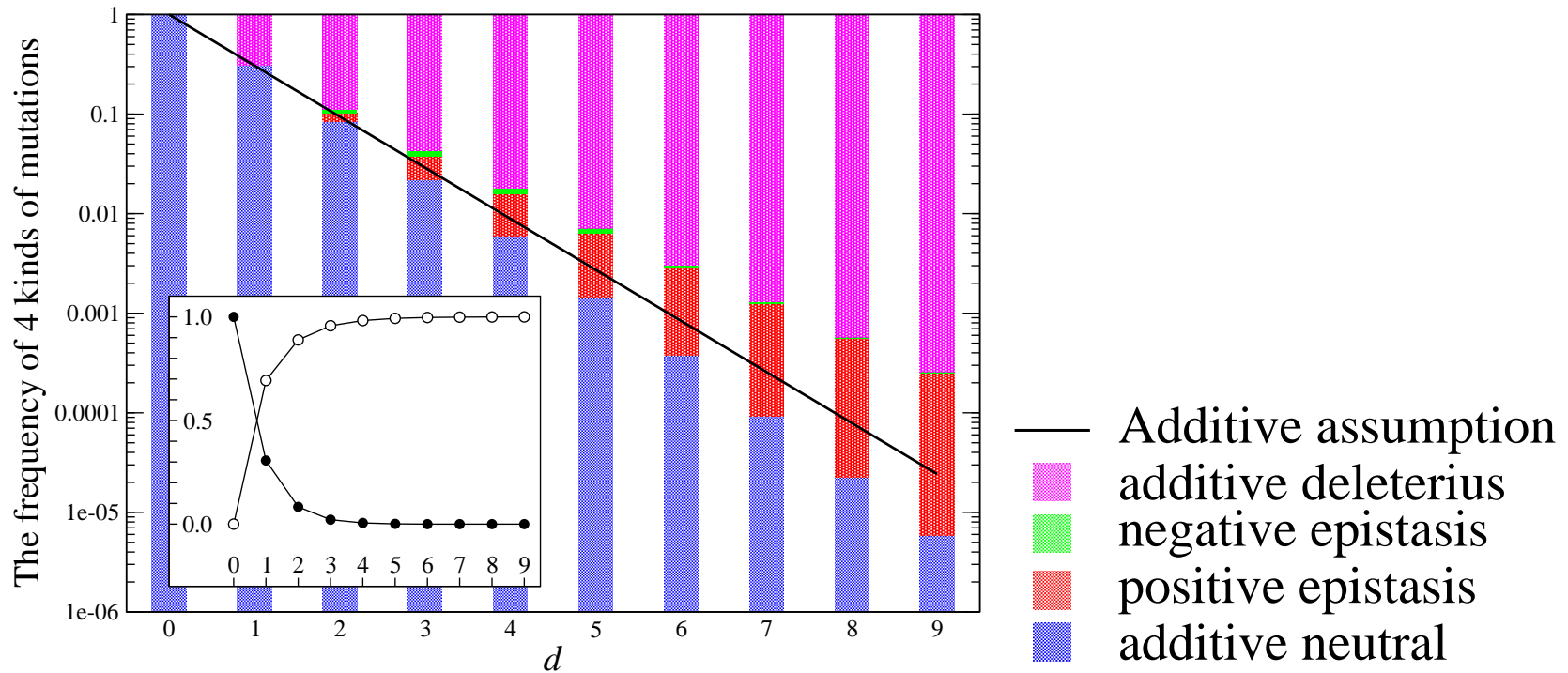
Phenotypic Information-threshold



Phenotypic Information-threshold



How epistatic RNA folding is?



| | a mutant is | |
|--------------|--------------------|----------------------|
| | neutral | deleterious |
| $\delta = 0$ | additive neutral | negative epistasis |
| $\delta > 0$ | positive epistasis | additive deleterious |

$\delta = \#$ deleterious substitutions



Positive epistasis occurs more frequently?

| | a mutant is | |
|--------------|--------------------|----------------------|
| | neutral | deleterious |
| $\delta = 0$ | additive neutral | negative epistasis |
| $\delta > 0$ | positive epistasis | additive deleterious |

Positive epistasis occurs more frequently?

| | a mutant is (at $d = 5$) | |
|--------------|---------------------------|---------------|
| | neutral | deleterious |
| $\delta = 0$ | 70% | 30% (neg epi) |
| $\delta > 0$ | 0.5% (pos epi) | 99.5% |

Positive epistasis occurs more frequently?

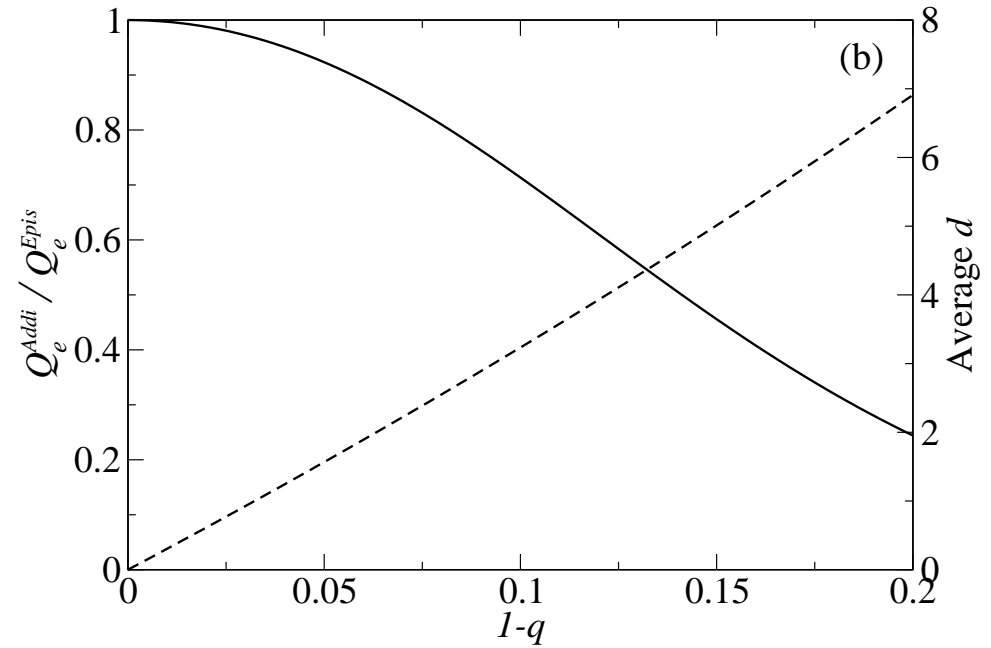
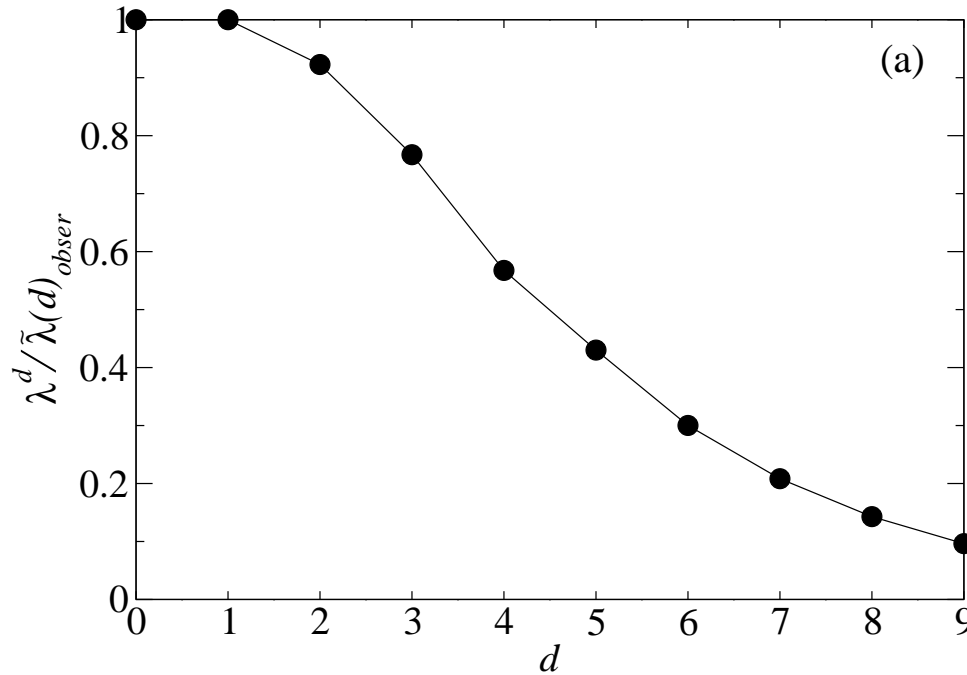
When $d = 5$, $\text{Prob}(\delta = 0) = \lambda^d = 0.3^5$

| | Prob |
|--------------|-------|
| $\delta = 0$ | 0.1% |
| $\delta > 0$ | 99.9% |

Positive epistasis occurs more frequently?

| | Prob | a mutant is ($d = 5$) | |
|--------------|-------|-------------------------|---------------|
| | | neutral | deleterious |
| $\delta = 0$ | 0.1% | 70% | 30% (neg epi) |
| $\delta > 0$ | 99.9% | 0.5% (pos epi) | 99.5% |

Why does additive assumption work?



- [L.] Average # of substitutions/replication is 3.8 at err. threshold ($1 - q = 0.05; N = 76$). Additive assumption underestimates prob. neutral replication.
- [R.] Average # of subs./neutral replication is 1.5 at err. thre. Thus, additive assumption will be correct.

Conclusions



- The phenotypic error-threshold was formulated analytically with the additive assumption.
- The formulation showed that mutational neutrality increases the error threshold but the increase is limited due to the multiple substitutions.
- The additive assumption can estimate err-thr. because the average number of substitutions per *neutral* replication is small enough to avoid of the effect of epistasis

